

\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 09:00:54 ON 20 MAY 2002

=> fil .bec,canc  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.21	0.21

FULL ESTIMATED COST

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,  
ESBIOBASE, BIOTECHNO, WPIDS, CANCERLIT' ENTERED AT 09:01:09 ON 20 MAY 2002  
ALL COPYRIGHTS AND RESTRICTIONS APPLY. SEE HELP USAGETERMS FOR DETAILS.

12 FILES IN THE FILE LIST

=> s carboxylesterase#  
FILE 'MEDLINE'  
L1 1579 CARBOXYLESTERASE#

FILE 'SCISEARCH'  
L2 1238 CARBOXYLESTERASE#

FILE 'LIFESCI'  
L3 623 CARBOXYLESTERASE#

FILE 'BIOTECHDS'  
L4 160 CARBOXYLESTERASE#

FILE 'BIOSIS'  
L5 1530 CARBOXYLESTERASE#

FILE 'EMBASE'  
L6 1631 CARBOXYLESTERASE#

FILE 'HCAPLUS'  
L7 2125 CARBOXYLESTERASE#

FILE 'NTIS'  
L8 54 CARBOXYLESTERASE#

FILE 'ESBIOBASE'  
L9 409 CARBOXYLESTERASE#

FILE 'BIOTECHNO'  
L10 482 CARBOXYLESTERASE#

FILE 'WPIDS'  
L11 36 CARBOXYLESTERASE#

FILE 'CANCERLIT'  
L12 217 CARBOXYLESTERASE#

TOTAL FOR ALL FILES  
L13 10084 CARBOXYLESTERASE#

=> s cpt-11 or irinotecan  
FILE 'MEDLINE'  
3065 CPT  
504200 11

828 CPT-11  
    (CPT(W) 11)  
1270 IRINOTECAN  
L14 1416 CPT-11 OR IRINOTECAN

FILE 'SCISEARCH'  
    3531 CPT  
    364410 11  
    945 CPT-11  
        (CPT(W) 11)  
    1061 IRINOTECAN  
L15 1398 CPT-11 OR IRINOTECAN

FILE 'LIFESCI'  
    490 "CPT"  
    63535 "11"  
    61 CPT-11  
        ("CPT" (W) "11")  
    49 IRINOTECAN  
L16 90 CPT-11 OR IRINOTECAN

FILE 'BIOTECHDS'  
    21 CPT  
    19822 11  
    3 CPT-11  
        (CPT(W) 11)  
    3 IRINOTECAN  
L17 4 CPT-11 OR IRINOTECAN

FILE 'BIOSIS'  
    2984 CPT  
    426155 11  
    831 CPT-11  
        (CPT(W) 11)  
    859 IRINOTECAN  
L18 1251 CPT-11 OR IRINOTECAN

FILE 'EMBASE'  
    3332 "CPT"  
    299980 "11"  
    1232 CPT-11  
        ("CPT" (W) "11")  
    2465 IRINOTECAN  
L19 2514 CPT-11 OR IRINOTECAN

FILE 'HCAPLUS'  
    3492 CPT  
    738788 11  
    652 CPT-11  
        (CPT(W) 11)  
    728 IRINOTECAN  
L20 1087 CPT-11 OR IRINOTECAN

FILE 'NTIS'  
    479 CPT  
    50247 11  
    1 CPT-11  
        (CPT(W) 11)  
    1 IRINOTECAN

L21 1 CPT-11 OR IRINOTECAN

FILE 'ESBIOBASE'

1339 CPT

105180 11

430 CPT-11

(CPT(W) 11)

510 IRINOTECAN

L22 678 CPT-11 OR IRINOTECAN

FILE 'BIOTECHNO'

753 CPT

75550 11

250 CPT-11

(CPT(W) 11)

416 IRINOTECAN

L23 440 CPT-11 OR IRINOTECAN

FILE 'WPIDS'

213 CPT

1221419 11

38 CPT-11

(CPT(W) 11)

74 IRINOTECAN

L24 102 CPT-11 OR IRINOTECAN

FILE 'CANCERLIT'

1504 CPT

138493 11

1016 CPT-11

(CPT(W) 11)

1209 IRINOTECAN

L25 1478 CPT-11 OR IRINOTECAN

TOTAL FOR ALL FILES

L26 10459 CPT-11 OR IRINOTECAN

=> s l13 and l26

FILE 'MEDLINE'

L27 56 L1 AND L14

FILE 'SCISEARCH'

L28 76 L2 AND L15

FILE 'LIFESCI'

L29 6 L3 AND L16

FILE 'BIOTECHDS'

L30 2 L4 AND L17

FILE 'BIOSIS'

L31 67 L5 AND L18

FILE 'EMBASE'

L32 68 L6 AND L19

FILE 'HCAPLUS'

L33 54 L7 AND L20

FILE 'NTIS'  
L34 0 L8 AND L21

FILE 'ESBIOBASE'  
L35 47 L9 AND L22

FILE 'BIOTECHNO'  
L36 25 L10 AND L23

FILE 'WPIDS'  
L37 1 L11 AND L24

FILE 'CANCERLIT'  
L38 53 L12 AND L25

TOTAL FOR ALL FILES  
L39 455 L13 AND L26

=> s l39 not 2000-2002/py  
FILE 'MEDLINE'  
1133053 2000-2002/PY  
L40 38 L27 NOT 2000-2002/PY

FILE 'SCISEARCH'  
2223288 2000-2002/PY  
L41 46 L28 NOT 2000-2002/PY

FILE 'LIFESCI'  
212923 2000-2002/PY  
L42 5 L29 NOT 2000-2002/PY

FILE 'BIOTECHDS'  
30370 2000-2002/PY  
L43 1 L30 NOT 2000-2002/PY

FILE 'BIOSIS'  
1178133 2000-2002/PY  
L44 44 L31 NOT 2000-2002/PY

FILE 'EMBASE'  
1000087 2000-2002/PY  
L45 47 L32 NOT 2000-2002/PY

FILE 'HCAPLUS'  
2208305 2000-2002/PY  
L46 36 L33 NOT 2000-2002/PY

FILE 'NTIS'  
0 2000-2002/PY  
L47 0 L34 NOT 2000-2002/PY

FILE 'ESBIOBASE'  
637039 2000-2002/PY  
L48 31 L35 NOT 2000-2002/PY

FILE 'BIOTECHNO'  
270062 2000-2002/PY  
L49 19 L36 NOT 2000-2002/PY

FILE 'WPIDS'  
1946425 2000-2002/PY  
L50 0 L37 NOT 2000-2002/PY

FILE 'CANCERLIT'  
109584 2000-2002/PY  
L51 46 L38 NOT 2000-2002/PY

TOTAL FOR ALL FILES  
L52 313 L39 NOT 2000-2002/PY

=> dup rem l52  
PROCESSING COMPLETED FOR L52  
L53 83 DUP REM L52 (230 DUPLICATES REMOVED)

=> d tot

L53 ANSWER 1 OF 83 CANCERLIT  
TI Metabolism of SN-38 by CYP3A4 and Microsomes from Human Liver (HLM).  
(Meeting abstract).  
SO Proc Annu Meet Am Soc Clin Oncol, (1999). Vol. 18, pp. A676.  
AU Shepard Dale; Ramirez Jacki; Iyer Lalith; Ratain Mark  
AN 1999700672 CANCERLIT

L53 ANSWER 2 OF 83 CANCERLIT  
TI Phase I and Pharmacokinetic (PK) Study of **Irinotecan** (**CPT-11**) in Cancer Patients (pts) with Hepatic Dysfunction (Meeting abstract).  
SO Proc Annu Meet Am Soc Clin Oncol, (1999). Vol. 18, pp. A634.  
AU Raymond E; Vernillet L; Boige V; Hua A; Ducreux M; Faivre S; Jacques C; Gatineau M; Mignard D; Vergniol J C; Rixe O; Armand J P  
AN 1999700630 CANCERLIT

L53 ANSWER 3 OF 83 CANCERLIT  
TI Role of the Gut Flora (IBF) in the Intestinal Toxicity from **CPT-11** in Mice. (Meeting abstract).  
SO Proc Annu Meet Am Soc Clin Oncol, (1999). Vol. 18, pp. A1068.  
AU Brandi Giovann; Dabar Jea; Biasco Guid; Raibaud Pierr; Bridonneau Chanta; Poggi Barbar; Pisi Annamari; Tamberi Stefan; Comis Silvi; Tura Sant  
AN 1999701063 CANCERLIT

L53 ANSWER 4 OF 83 MEDLINE DUPLICATE 1  
TI Water soluble 20(S)-glycinate esters of 10,11-methylenedioxycamptothecins are highly active against human breast cancer xenografts.  
SO CANCER RESEARCH, (1999 Jul 15) 59 (14) 3424-8.  
Journal code: CNF; 2984705R. ISSN: 0008-5472.  
AU Wadkins R M; Potter P M; Vladu B; Marty J; Mangold G; Weitman S; Manikumar G; Wani M C; Wall M E; Von Hoff D D  
AN 1999342994 MEDLINE

L53 ANSWER 5 OF 83 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 2  
TI In vitro activation of **irinotecan** to SN-38 by human liver and intestine  
SO ANTICANCER RESEARCH, (MAY-JUN 1999) Vol. 19, No. 3A, pp. 2067-2071.  
Publisher: INT INST ANTICANCER RESEARCH, EDITORIAL OFFICE 1ST KM KAPANDNTIOU-KALAMOU RD KAPANDRITI, POB 22, ATHENS 19014, GREECE.  
ISSN: 0250-7005.  
AU Ahmed F; Vyas V; Cornfield A; Goodin S; Ravikumar T S; Rubin E H; Gupta E (Reprint)

AN 1999:628669 SCISEARCH

L53 ANSWER 6 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.  
TI Sequence-dependent growth inhibition and DNA damage formation by the  
**irinotecan**-5-fluorouracil combination in human colon carcinoma  
cell lines.

SO European Journal of Cancer, (1999) 35/13 (1851-1861).  
Refs: 51

ISSN: 0959-8049 CODEN: EJCAEL

AU Mans D.R.A.; Grivicich I.; Peters G.J.; Schwartzmann G.

AN 1999380287 EMBASE

L53 ANSWER 7 OF 83 SCISEARCH COPYRIGHT 2002 ISI (R)

TI The anticancer prodrug **CPT-11** is a potent inhibitor of  
acetylcholinesterase but is rapidly catalyzed to SN-38 by  
butyrylcholinesterase

SO CANCER RESEARCH, (1 APR 1999) Vol. 59, No. 7, pp. 1458-1463.  
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202.  
ISSN: 0008-5472.

AU Morton C L; Wadkins R M; Danks M K; Potter P M (Reprint)

AN 1999:274520 SCISEARCH

L53 ANSWER 8 OF 83 MEDLINE DUPLICATE 3

TI Comparison of activation of **CPT-11** by rabbit and human  
**carboxylesterases** for use in enzyme/prodrug therapy.

SO CLINICAL CANCER RESEARCH, (1999 Apr) 5 (4) 917-24.  
Journal code: C2H; 9502500. ISSN: 1078-0432.

AU Danks M K; Morton C L; Krull E J; Cheshire P J; Richmond L B; Naeve C W;  
Pawlik C A; Houghton P J; Potter P M

AN 1999228217 MEDLINE

L53 ANSWER 9 OF 83 SCISEARCH COPYRIGHT 2002 ISI (R)

TI Virus-directed enzyme prodrug therapy (VDEPT) with **CPT-11**  
and rabbit **carboxylesterase** for purging of tumor  
cells from stem cells for autologous transplant of patients with  
neuroblastoma.

SO CLINICAL CANCER RESEARCH, (NOV 1999) Vol. 5, Supp. [S], pp. 509-509.  
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202.  
ISSN: 1078-0432.

AU Meck M M (Reprint); Harris L C; Potter P M; Danks M K

AN 1999:965134 SCISEARCH

L53 ANSWER 10 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V. DUPLICATE 4

TI Recent developments in gene-directed enzyme prodrug therapy (GDEPT) for  
cancer.

SO Current Opinion in Molecular Therapeutics, (1999) 1/4 (480-486).  
Refs: 61

ISSN: 1464-8431 CODEN: CUOTFO

AU Niculescu-Duvaz I.; Cooper R.G.; Stribbling S.M.; Heyes J.A.; Metcalfe  
J.A.; Springer C.J.

AN 1999312780 EMBASE

L53 ANSWER 11 OF 83 MEDLINE DUPLICATE 5

TI **CPT-11** converting **carboxylesterase** and  
topoisomerase activities in tumour and normal colon and liver tissues.

SO BRITISH JOURNAL OF CANCER, (1999 May) 80 (3-4) 364-70.  
Journal code: AV4; 0370635. ISSN: 0007-0920.

AU Guichard S; Terret C; Hennebelle I; Lochon I; Chevreau P; Fretigny E;  
Selves J; Chatelut E; Bugat R; Canal P

AN 1999314758 MEDLINE

L53 ANSWER 12 OF 83 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

TI **CPT-11** converting **carboxylesterase** in tumor  
and normal colon and liver tissues.

SO Proceedings of the American Association for Cancer Research Annual  
Meeting, (March, 1999) Vol. 40, pp. 340.  
Meeting Info.: 90th Annual Meeting of the American Association for Cancer  
Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American  
Association for Cancer Research  
. ISSN: 0197-016X.

AU Guichard, S.; Hennebelle, I.; Chevreau, P.; Fretigny, E.; Selves, J.;  
Bugat, R.; Canal, P.

AN 1999:179140 BIOSIS

L53 ANSWER 13 OF 83 MEDLINE DUPLICATE 6

TI High-performance liquid chromatographic method for the simultaneous  
determination of the camptothecin derivative **irinotecan**  
hydrochloride, **CPT-11**, and its metabolites SN-38 and  
SN-38 glucuronide in rat plasma with a fully automated on-line solid-phase  
extraction system, PROSPEKT.

SO JOURNAL OF CHROMATOGRAPHY. B, BIOMEDICAL SCIENCES AND APPLICATIONS, (1999  
Mar 19) 724 (2) 335-44.

Journal code: CXN; 9714109. ISSN: 1387-2273.

AU Kurita A; Kaneda N

AN 1999236416 MEDLINE

L53 ANSWER 14 OF 83 SCISEARCH COPYRIGHT 2002 ISI (R)

TI Propionate and butyrate esters of camptothecin and 9-nitrocamptothecin as  
antileukemia prodrugs in vitro

SO EUROPEAN JOURNAL OF HAEMATOLOGY, (APR 1999) Vol. 62, No. 4, pp. 246-255.  
Publisher: MUNKSGAARD INT PUBL LTD, 35 NORRE SOGADE, PO BOX 2148, DK-1016  
COPENHAGEN, DENMARK.  
ISSN: 0902-4441.

AU Han Z; Cao Z; Chatterjee D; Wyche J; Pantazis P (Reprint)

AN 1999:300165 SCISEARCH

L53 ANSWER 15 OF 83 MEDLINE DUPLICATE 7

TI Effective **irinotecan (CPT-11)**-containing  
liposomes: intraliposomal conversion to the active metabolite SN-38.

SO JAPANESE JOURNAL OF CANCER RESEARCH, (1999 Feb) 90 (2) 226-32.  
Journal code: HBA; 8509412. ISSN: 0910-5050.

AU Sadzuka Y; Hirotsu S; Hirota S

AN 1999205892 MEDLINE

L53 ANSWER 16 OF 83 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

TI **CPT-11** is an inhibitor of acetylcholinesterase but can  
be activated to SN-38 by butyrylcholinesterases.

SO Proceedings of the American Association for Cancer Research Annual  
Meeting, (March, 1999) Vol. 40, pp. 210.  
Meeting Info.: 90th Annual Meeting of the American Association for Cancer  
Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American  
Association for Cancer Research  
. ISSN: 0197-016X.

AU Potter, P. M. (1); Morton, C. L.; Wadkins, R. M.; Danks, M. K.

AN 1999:226707 BIOSIS

L53 ANSWER 17 OF 83 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

TI Enhanced cytotoxicity to **CPT-11** due to the bystander

effect by cells expressing a secreted form of a rabbit liver  
**carboxylesterase**.

- SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 210.  
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American Association for Cancer Research  
. ISSN: 0197-016X.
- AU Wierdl, M.; Morton, C. L.; Danks, M. K.; Pötter, P. M.  
AN 1999:226709 BIOSIS

- L53 ANSWER 18 OF 83 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
TI Human plasma **irinotecan carboxylesterase** converting enzyme activity in patients receiving infusional **irinotecan**.
- SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 210.  
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American Association for Cancer Research  
. ISSN: 0197-016X.
- AU Guemei, A. (1); Cottrell, J.; Band, R.; Prudhomme, M.; Bowen, D.; Taylor, R. E.; Hamilton, J. M.; Monahan, B. M.; Allegra, C. J.; Grem, J. L.; Takimoto, C. H.  
AN 1999:226708 BIOSIS

- L53 ANSWER 19 OF 83 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
TI Comparison of the efficiency of **CPT-11** activation by a rabbit and a human **carboxylesterase** for use in enzyme/prodrug therapy.
- SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 110.  
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American Association for Cancer Research  
. ISSN: 0197-016X.
- AU Danks, M. K.; Morton, C. L.; Krull, E. J.; Cheshire, P. J.; Richmond, L. B.; Pawlik, C. A.; Houghton, P. J.; Potter, P. M.  
AN 1999:184520 BIOSIS

- L53 ANSWER 20 OF 83 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
TI N-MYC-mediated overexpression of a **CPT-11**-activating enzyme in neuroblastoma cells.
- SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 110.  
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American Association for Cancer Research  
. ISSN: 0197-016X.
- AU Pawlik, C. A.; Iyengar, R. V.; Krull, E. J.; Harris, L. C.; Potter, P. M.; Danks, M. K.; Guichard, S. M.  
AN 1999:184521 BIOSIS

- L53 ANSWER 21 OF 83 MEDLINE DUPLICATE 8  
TI In vivo and ex vivo gene therapy strategies to treat tumors using adenovirus gene transfer vectors.
- SO CANCER CHEMOTHERAPY AND PHARMACOLOGY, (1999) 43 Suppl S90-9. Ref: 107  
Journal code: C9S; 7806519. ISSN: 0344-5704.
- AU Crystal R G  
AN 1999284458 MEDLINE



L53 ANSWER 22 OF 83 Elsevier BIOBASE COPYRIGHT 2002 Elsevier Science B.V.  
 DUPLICATE  
 AN 1999121567 ESBIODASE  
 TI In vivo and ex vivo gene therapy strategies to treat tumors using  
 adenovirus gene transfer vectors  
 AU Crystal R.G.  
 CS R.G. Crystal, ST 505, 520 East 70th Street, New York, NY 10021, United  
 States.  
 E-mail: geneticmedicine@mail.med.cornell.edu  
 SO Cancer Chemotherapy and Pharmacology, Supplement, (1999), 43/- (S90-S99),  
 107 reference(s)  
 CODEN: CCHSET ISSN: 0943-9404  
 DT Journal; Conference Article  
 CY Germany, Federal Republic of  
 LA English  
 SL English

L53 ANSWER 23 OF 83 SCISEARCH COPYRIGHT 2002 ISI (R)  
 TI Use of rabbit **carboxylesterase/CPT-11** in a  
 virus-directed enzyme prodrug approach (VDEPT) to purging of neuroblastoma  
 cells from human hematopoietic cells before autologous stem cell rescue  
 SO CANCER GENE THERAPY, (NOV-DEC 1999) Vol. 6, No. 6, Supp. [S], pp. 066-066.  
 Publisher: STOCKTON PRESS, 345 PARK AVE SOUTH, NEW YORK, NY 10010-1707.  
 ISSN: 0929-1903.  
 AU Danks M K (Reprint); Meck M M; Harris L C; Potter P M  
 AN 2000:4532 SCISEARCH

L53 ANSWER 24 OF 83 CANCERLIT  
 TI **CPT-11-DOXORUBICIN (DXR) COMBINATION IN ADVANCED**  
**NON-SMALL CELL LUNG CANCER (NSCLC). A PILOT STUDY BASED ON IN VITRO**  
**EXPERIMENTS (Meeting abstract).**  
 SO Proc Annu Meet Am Soc Clin Oncol, (1998). Vol. 17, pp. A1935.  
 AU Takaoka K; Inoue S; Ohtsuka K; Shida A; Araya Y; Ito M  
 AN 1998701932 CANCERLIT

L53 ANSWER 25 OF 83 MEDLINE DUPLICATE 10  
 TI Reversal of **CPT-11** resistance of lung cancer cells by  
 adenovirus-mediated gene transfer of the human **carboxylesterase**  
 cDNA.  
 SO CANCER RESEARCH, (1998 Oct 1) 58 (19) 4368-74.  
 Journal code: CNF; 2984705R. ISSN: 0008-5472.  
 AU Kojima A; Hackett N R; Crystal R G  
 AN 1998438056 MEDLINE

L53 ANSWER 26 OF 83 MEDLINE DUPLICATE 11  
 TI Cellular localization domains of a rabbit and a human  
**carboxylesterase: influence on irinotecan (CPT**  
**-11) metabolism by the rabbit enzyme.**  
 SO CANCER RESEARCH, (1998 Aug 15) 58 (16) 3627-32.  
 Journal code: CNF; 2984705R. ISSN: 0008-5472.  
 AU Potter P M; Wolverton J S; Morton C L; Wierdl M; Danks M K  
 AN 1998387326 MEDLINE

L53 ANSWER 27 OF 83 MEDLINE DUPLICATE 12  
 TI Conversion of the **CPT-11** metabolite APC to SN-38 by  
 rabbit liver **carboxylesterase.**  
 SO CLINICAL CANCER RESEARCH, (1998 Dec) 4 (12) 3089-94.  
 Journal code: C2H; 9502500. ISSN: 1078-0432.

AU Guichard S M; Morton C L; Krull E J; Stewart C F; Danks M K; Potter P M  
AN 1999081523 MEDLINE

L53 ANSWER 28 OF 83 MEDLINE DUPLICATE 13  
TI Pathophysiology and therapy of **irinotecan**-induced delayed-onset diarrhea in patients with advanced colorectal cancer: a prospective assessment.  
SO JOURNAL OF CLINICAL ONCOLOGY, (1998 Aug) 16 (8) 2745-51.  
Journal code: JCO; 8309333. ISSN: 0732-183X.  
AU Saliba F; Hagipantelli R; Misset J L; Bastian G; Vassal G; Bonnay M; Herait P; Cote C; Mahjoubi M; Mignard D; Cvitkovic E  
AN 1998368425 MEDLINE

L53 ANSWER 29 OF 83 MEDLINE DUPLICATE 14  
TI Isolation and partial characterization of a cDNA encoding a rabbit liver **carboxylesterase** that activates the prodrug **irinotecan** (CPT-11).  
SO CANCER RESEARCH, (1998 Jun 15) 58 (12) 2646-51.  
Journal code: CNF; 2984705R. ISSN: 0008-5472.  
AU Potter P M; Pawlik C A; Morton C L; Naeve C W; Danks M K  
AN 1998297515 MEDLINE

L53 ANSWER 30 OF 83 MEDLINE DUPLICATE 15  
TI Determinants of **CPT-11** and SN-38 activities in human lung cancer cells.  
SO BRITISH JOURNAL OF CANCER, (1998 Jun) 77 (12) 2171-6.  
Journal code: AV4; 0370635. ISSN: 0007-0920.  
AU van Ark-Otte J; Kedde M A; van der Vijgh W J; Dingemans A M; Jansen W J; Pinedo H M; Boven E; Giaccone G  
AN 1998311463 MEDLINE

L53 ANSWER 31 OF 83 MEDLINE DUPLICATE 16  
TI In vivo human **carboxylesterase** cDNA gene transfer to activate the prodrug **CPT-11** for local treatment of solid tumors.  
SO JOURNAL OF CLINICAL INVESTIGATION, (1998 Apr 15) 101 (8) 1789-96.  
Journal code: HS7; 7802877. ISSN: 0021-9738.  
AU Kojima A; Hackett N R; Ohwada A; Crystal R G  
AN 1998210118 MEDLINE

L53 ANSWER 32 OF 83 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 17  
TI Pharmacology of **irinotecan**  
SO DRUGS OF TODAY, (SEP 1998) Vol. 34, No. 9, pp. 777-803.  
Publisher: PROUS SCIENCE, SA, PO BOX 540, PROVENZA 388, 08025 BARCELONA, SPAIN.  
ISSN: 0025-7656.  
AU Robert J (Reprint); Rivory L  
AN 1998:867161 SCISEARCH

L53 ANSWER 33 OF 83 SCISEARCH COPYRIGHT 2002 ISI (R)  
TI Studies of the efficacy and pharmacology of **irinotecan** against human colon tumor xenograft models  
SO CLINICAL CANCER RESEARCH, (MAR 1998) Vol. 4, No. 3, pp. 743-753.  
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202.  
ISSN: 1078-0432.  
AU Zamboni W C; Stewart C F; Cheshire P J; Richmond L B; Hanna S K; Luo X L; Poquette C; McGovren J P; Houghton J A; Houghton P J (Reprint)  
AN 1998:232591 SCISEARCH

L53 ANSWER 34 OF 83 MEDLINE DUPLICATE 18  
 TI Identification of a new metabolite of **CPT-11** (**irinotecan**): pharmacological properties and activation to SN-38.  
 SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1998 Jul) 286 (1) 578-83.  
 Journal code: JP3; 0376362. ISSN: 0022-3565.  
 AU Dodds H M; Haaz M C; Riou J F; Robert J; Rivory L P  
 AN 1998330572 MEDLINE

L53 ANSWER 35 OF 83 MEDLINE DUPLICATE 19  
 TI Altered **irinotecan** and SN-38 disposition after intravenous and oral administration of **irinotecan** in mice bearing human neuroblastoma xenografts.  
 SO CLINICAL CANCER RESEARCH, (1998 Feb) 4 (2) 455-62.  
 Journal code: C2H; 9502500. ISSN: 1078-0432.  
 AU Zamboni W C; Houghton P J; Thompson J; Cheshire P J; Hanna S K; Richmond L B; Lou X; Stewart C F  
 AN 1998177580 MEDLINE

L53 ANSWER 36 OF 83 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 TI Isolation and characterization of a cDNA encoding a rabbit **carboxylesterase** that converts **CPT-11** to SN-38.  
 SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1998) Vol. 39, pp. 421.  
 Meeting Info.: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998 American Association for Cancer Research  
 . ISSN: 0197-016X.  
 AU Potter, P. M.; Pawlik, C. A.; Morton, C. M.; Danks, M. K.  
 AN 1998:196739 BIOSIS

L53 ANSWER 37 OF 83 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 TI Epitope-tagged rabbit liver **carboxylesterase** confers sensitivity to **CPT-11** and localizes to the endoplasmic reticulum.  
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 Meeting Info.: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998 American Association for Cancer Research  
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L53 ANSWER 82 OF 83 HCAPLUS COPYRIGHT 2002 ACS  
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L53 ANSWER 83 OF 83 MEDLINE DUPLICATE 44  
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L53 ANSWER 10 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 4  
AB Gene-directed enzyme prodrug therapy (GDEPT) is a promising two-step treatment for solid malignant tumors. In the first step, the gene for a foreign enzyme is administered and directed to the tumor, where it may be expressed using specific transcriptional elements. In the second step, prodrugs are administered and activated by the foreign enzyme expressed at the tumor. This review focuses on the progress from the end of 1997 to date. Important issues, such as viral and non-viral vectors, new enzyme/prodrug systems, new strategies, advances in the understanding of the bystander effects, the comparison of different systems used in GDEPT and clinical trials are outlined.

L53 ANSWER 21 OF 83 MEDLINE DUPLICATE 8  
AB The adaptation of gene therapy strategies to treat tumors has broadened the potential armamentarium of anticancer strategies to include approaches for local control of tumor growth as well as to enhance systemic antitumor immunity to treat metastases. A major focus of the author and colleagues has been to use replication-deficient adenovirus vectors, both in vivo and ex vivo, to enhance local control of and systemic immunity against cancer. Several examples will be used to demonstrate these strategies. Using prodrugs, systemically administered drugs converted to toxic metabolites in the local tumor milieu, has proven to be a useful strategy for achieving high local concentrations of the toxic product while avoiding the systemic toxicity that limits the use of chemotherapy agents. Transfer of genes encoding cytosine deaminase (with 5-fluorocytosine) and **carboxylesterase** (CE) (with **irinotecan**) are two paradigms that have been used in our laboratory. The data demonstrate that using adenoviruses to deliver these genes to the tumor site leads to production of the active chemotherapeutic agent, which diffuses from the cell in which it was produced to suppress tumor growth and attain regional control in a single organ. Extensive experimental and clinical data now exist to support the concept that tumor growth is critically dependent on angiogenesis and that vascular endothelial growth factor (VEGF) appears to play a central role in the process of tumor neovascularization. Data generated in our laboratory have shown that adenovirus-mediated regional anti-VEGF therapy using a gene encoding a soluble form of flt-1 (one of the VEGF receptors) can be used for regional control of tumor growth. The critical dependence of many tumors on VEGF for neovascularization and dissemination predicts the general applicability of this strategy for treatment of many solid tumors. Another paradigm involves dendritic cells, potent antigen-presenting cells that play a critical role in the initiation of antitumor immune responses. Immunization of mice with dendritic cells genetically modified using an adenovirus vector transferring a gene encoding a tumor antigen confers potent protection against a lethal tumor challenge, as well as suppression of preestablished tumors, resulting in a significant survival advantage. One clinical scenario to which this approach is relevant is treating micrometastases present at the time of primary detection of many malignancies. A possible clinical strategy would be to modify dendritic cells from such patients using an adenovirus vector encoding the relevant tumor antigen, and then administering the genetically modified dendritic cells as adjuvant

treatment following primary therapy.

L53 ANSWER 26 OF 83 MEDLINE DUPLICATE 11  
AB Enzyme activation of prodrugs to improve the therapeutic index of specific anticancer agents is an attractive alternative to current chemotherapy regimens. This study addresses the potential for activating **irinotecan (CPT-11)** with recombinant **carboxylesterases** (CEs). CEs are a ubiquitous class of enzymes thought to be involved in the detoxification of xenobiotics. Their primary amino acid sequence indicates that these proteins should be localized to the endoplasmic reticulum. By PCR-mediated mutagenesis of a rabbit liver and a human alveolar macrophage CE cDNA, expression in Cos7 cells, and subsequent immunohistochemical localization, we have determined that an 18-amino acid NH2-terminal hydrophobic signal peptide is responsible for the localization of these proteins to the endoplasmic reticulum. By similar approaches, we have demonstrated that the COOH-terminal amino acids HIEL prevent secretion of the proteins from the cell. Enzymatic activity was lost by removing the NH2-terminal domain; however, active enzyme could be detected in the culture media of cells expressing the COOH-terminally truncated proteins. Secretion of CEs lacking the six COOH-terminal amino acids could be prevented with brefeldin A, confirming that these truncated enzymes were processed and released from cells by endoplasmic reticulum-mediated exocytosis. Double-truncation mutant enzymes lacking both NH2- and COOH-terminal sequences demonstrated immunostaining patterns similar to those of the NH2-terminally truncated proteins and also lacked CE activity. In all cases, metabolism of the classic esterase substrate o-nitrophenyl acetate predicted the sensitivity of cells expressing the rabbit CE to the anticancer agent **CPT-11**. In addition, the secreted enzyme sensitized Cos7 cells to this drug, indicating that protein association with a lipid bilayer is not required for substrate metabolism.

L53 ANSWER 27 OF 83 MEDLINE DUPLICATE 12  
AB The anticancer drug **CPT-11** (7-ethyl-[4(1-piperidino)-1-piperidino]carbonyloxycamptothecin) is a water-soluble derivative of camptothecin. We report here the conversion of APC (7-ethyl-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin), an inactive metabolite of **CPT-11**, to SN-38 (7-ethyl-10-hydroxycamptothecin), the active metabolite of **CPT-11**, by a rabbit liver **carboxylesterase**. This reaction is not catalyzed by any known human enzyme. The formation of SN-38 from APC was characterized by an apparent Km of 37.9 +/- 7.1 microM and a Vmax of 16.9 +/- 0.9 pmol/units/min. SN-38 was confirmed as a reaction product by high-performance liquid chromatography and mass spectrometry. A 24-h incubation of 10 microM APC with 500 units/ml of rabbit **carboxylesterase** produced 4 microM SN-38. The product of this reaction inhibited the growth of U373 MG human glioblastoma cells in vitro. The IC50 for a 24-h exposure of U373 MG cells to APC in the presence of 50 units/ml of rabbit **carboxylesterase** was 0.27 +/- 0.08 microM, whereas APC alone demonstrated no inhibition of growth at concentrations up to 1 microM. The IC50 of U373 MG cells transfected with the cDNA encoding the rabbit **carboxylesterase** (U373pIRESrabbit) and exposed to APC for 24 h was 0.8 +/- 0.1 microM APC, whereas the growth of cells transfected with vector control (U373pIRES) was unaffected by up to 1 microM APC. Because APC is nontoxic to human cells, we are investigating the possibility of using APC/rabbit **carboxylesterase** in a prodrug/enzyme therapeutic approach.

L53 ANSWER 29 OF 83 MEDLINE DUPLICATE 14

AB We have isolated a cDNA encoding a rabbit **carboxylesterase** (CE; EC 3.1.1.1) that converts the camptothecin-derived prodrug **irinotecan** (**CPT-11**) to the potent topoisomerase I inhibitor 7-ethyl-10-hydroxycamptothecin. NH<sub>2</sub>-terminal amino acid sequencing of a purified rabbit CE allowed the design of redundant oligonucleotides to perform PCR from rabbit liver cDNA. DNA sequencing of the PCR product confirmed the identity of the clone, and after both 5' and 3' rapid amplification of cDNA ends, oligonucleotide primers were designed to amplify the entire cDNA. The 1698-bp open reading frame encoded a 565-amino acid protein containing the characteristic CE B-1 and B-2 motifs, a hydrophobic NH<sub>2</sub>-terminal leader sequence, and the COOH-terminal residues HIEL that are thought to be responsible for protein localization in the endoplasmic reticulum. Transient expression of the cDNA in COS-7 cells resulted in CE activity in cell extracts and increased the sensitivity of cells to **CPT-11**. Additionally, stable expression of the rabbit liver CE cDNA in the human glioma U-373 MG cell line resulted in a 56-fold decrease in the IC<sub>50</sub> value for **CPT-11**, whereas the expression of a human alveolar macrophage cDNA encoding a highly homologous CE produced no change in drug sensitivity.

L53 ANSWER 30 OF 83 MEDLINE DUPLICATE 15

AB **Irinotecan** (**CPT-11**) is a semisynthetic camptothecin derivative with a broad spectrum of anti-tumour activity. **Carboxylesterase** (CE) catalyses the conversion of **CPT-11** to SN-38 (7-ethyl-10-hydroxycamptothecin), the active form of **CPT-11**. The antiproliferative effects of **CPT-11** and SN-38, CE-activity and topoisomerase I protein expression were investigated in five human small-cell lung cancer (SCLC) cell lines and four human non-small-cell lung cancer (NSCLC) cell lines. Antiproliferative activity, expressed as IC<sub>50</sub> values, was determined using the MTT assay. **CPT-11** was significantly more active in SCLC than in NSCLC cell lines ( $P = 0.0036$ ), whereas no significant difference between histological types was observed with SN-38. A significant correlation ( $r^2 = 0.52$ ,  $P = 0.028$ ) was observed between CE activity and chemosensitivity to **CPT-11** but not to SN-38, and significantly higher CE activity was observed in SCLC compared with NSCLC cell lines ( $P = 0.025$ ). Western blotting experiments showed topoisomerase I protein expressions within a factor of 2, and a granular nuclear staining was detectable in all cell lines by immunocytochemistry of cytopspins. No correlation was observed between protein expression and sensitivity to **CPT-11** or SN-38. Cellular and medium concentrations of **CPT-11** and SN-38 were measured by high-performance liquid chromatography (HPLC) in one SCLC cell line with high CE activity and high sensitivity to **CPT-11**, and one NSCLC cell line with low sensitivity to **CPT-11** and CE activity. Intracellular concentrations of **CPT-11** and SN-38 were higher in the SCLC cell line, and this was associated with an increase in cellular uptake of **CPT-11** compared with the medium, and an increased intracellular formation of SN-38. In conclusion, CE activity appears to be associated with higher sensitivity to **CPT-11** in human lung cancer cell lines and may partly explain the difference in the in vitro sensitivity to **CPT-11** between SCLC and NSCLC cells. The assessment of CE activity in clinical material of lung cancer patients undergoing treatment with **CPT-11** may be warranted. However, other mechanisms may influence sensitivity to **CPT-11**, possibly including drug transport.

L53 ANSWER 31 OF 83 MEDLINE DUPLICATE 16

AB To evaluate the concept that in vivo transfer of the human **carboxylesterase** gene will confer sensitivity of a solid tumor to the prodrug **CPT-11** (**irinotecan**), we constructed an adenovirus vector (AdCMV.CE) carrying the human **carboxylesterase** gene driven by the cytomegalovirus (CMV) promoter, infected A549 human lung adenocarcinoma cells in vitro and in vivo, and evaluated cell growth over time. AdCMV.CE produced a functional **carboxylesterase** protein in A549 cells in vitro and in vivo as evidenced by ability of lysates from the infected cells to convert **CPT-11** to its active metabolite SN-38. The AdCMV.CE vector effectively suppressed A549 cell growth in vitro in the presence of **CPT-11**. Cell mixing studies demonstrated that when as few as 10% of cells expressed the human **carboxylesterase** gene, there was bystander growth suppression in the presence of **CPT-11**. Consistent with these in vitro observations, when AdCMV.CE was directly injected into established subcutaneous A549 tumors in nude mice receiving **CPT-11**, there was 35% reduction in tumor size at day 27 compared to controls, and a 41% reduction at day 34 ( $P < 0.01$ , both comparisons to controls). Similar observations were made with the cell line H157 and HeLa. These observations suggest that local gene transfer of the human **carboxylesterase** gene and concomitant local administration of **CPT-11** may have potential as a strategy for control of the growth of solid tumors.

L53 ANSWER 32 OF 83 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 17

AB **Irinotecan** (CPT-II) is a semisynthetic derivative of camptothecin, an alkaloid extracted from the Chinese plant *Camptotheca acuminata*. It bears a bis-piperidine moiety and was selected for its water solubility and promising preclinical antitumor activity in in vitro and in vivo models. The target of drugs of the camptothecin family is DNA topoisomerase I, a nuclear enzyme involved in the relaxation of the DNA double helix required for replication and transcription activities. They stabilize the enzyme-DNA complex and prevent the religation of the single-strand breaks created by the enzyme, which are converted to double-strand breaks upon the collision with a replication fork during the S-phase. Resistance to **irinotecan** appears not to be mediated by P-glycoprotein, but by qualitative and/or quantitative alterations of its target, topoisomerase I, or by alterations occurring downstream of this interaction.

As with all camptothecin derivatives, **irinotecan** contains a lactone ring that can be spontaneously and reversibly hydrolyzed to a carboxylate open ring form, which predominates at neutral and alkaline pH and is inactive on topoisomerase I-DNA complexes. **Irinotecan** is, in fact, much less active than its metabolite SN-38 and is generally considered as a prodrug of this compound. The **carboxylesterase** which carries out this conversion is preferentially active on the lactone form of **irinotecan** and directly generates the lactone form of SN-38, which may explain the superiority of **irinotecan** over SN-38 in vivo. Further metabolism of SN-38 to a beta-glucuronide conjugate is a major pathway of detoxification and plays an important role in determining **irinotecan** toxicity in the clinical setting. Other metabolic pathways of **irinotecan** involve oxidations occurring on the bis-piperidine rings, which are carried out by cytochrome P450.

**Irinotecan** has shown an important activity in advanced and metastatic colorectal carcinoma and is now used for this indication in several countries, with two different recommended schedules: weekly administration of 125 mg/m<sup>2</sup> with a 2-week drug-free interval every 4 administrations or 3-weekly administration of 350 mg/m<sup>2</sup>, a dose that can be increased to 500 mg/m<sup>2</sup> with the support of antidiarrhetics. Other

possible indications of **irinotecan** include lung and cervix cancer, which are presently under investigation. The dose-limiting toxicity of **irinotecan** is mainly diarrhea, which occurs 7-10 days after treatment and can be life-threatening when associated with neutropenia, another frequent side effect. High-dose loperamide has shown good efficacy for treating this diarrhea and has allowed an increase in **irinotecan** doses tolerated by patients.

The pharmacokinetics of **irinotecan** are characterized by a 2- or 3-compartment decay, with a terminal half-life of about 10 h, a total volume of distribution of 150 l/m(2) and a total plasma clearance of 15 l/h/m(2). SN-38 AUC is only a small fraction of that of **irinotecan** (2-4%) and SN-38 is eliminated from plasma with a half-life of about 12 h. SN-38 glucuronide is present in plasma at higher concentrations than SN-38 and is eliminated at the same rate. APC, produced by the action of cytochrome P450, isoenzyme 3A4, is present in plasma at concentrations close to those of **irinotecan** itself. Only a small fraction of **irinotecan** and its metabolites is eliminated in urine and a higher proportion in the bile, with an enterohepatic cycle of SN-38 glucuronide and SN-38. Significant relationships have been established between the AUCs of both **irinotecan** and SN-38 and hematological and intestinal toxicities, suggesting a potential use for monitoring of this drug, (C) 1998 Prous Science. All rights reserved.

L53 ANSWER 33 OF 83 SCISEARCH COPYRIGHT 2002 ISI (R)

AB **Irinotecan**, administered i.v. on days 1-5 and 8-12 [(dx5)2 i.v.] has demonstrated significant activity against advanced human tumor xenografts. To explore the feasibility of prolonged oral administration of **irinotecan**, we compared the efficacy of oral and i.v. **irinotecan** on the (dx5)2 schedule. We also evaluated oral therapy for 12 consecutive weeks [(dx5)12] at 25 and 50 mg/kg and two consecutive 5-day courses repeated every 21 days for up to four cycles (r(dx5)2)4 at 50 and 75 mg/kg/dose in a series of human colon carcinoma xenograft lines. In addition, we evaluated the effect of a sensitive (HCl) and resistant (ELC2) human colon adenocarcinoma xenograft on **irinotecan** and SN-38 lactone disposition after administration of **irinotecan** 10 mg/kg i.v. and 10 and 25 mg/kg p.o. **Irinotecan** i.v. at 40 mg/kg and oral at 50 and 75 mg/kg on the (dx5)2 schedule had similar activity against the panel of adult colon adenocarcinoma xenografts. **Irinotecan** given p.o. also demonstrated significant activity against a topotecan-resistant derivative, VRC5/TOPO. Oral administration of 75 mg/kg r(dx5)2)4 and 50 mg/kg (dx5)12 achieved complete response in five of seven xenograft lines evaluated. After i.v. administration, mice bearing HCl xenografts had 43% greater SN-38 lactone systemic exposure compared to those with ELC2 xenografts and non-tumor-bearing mice. After oral (10 mg/kg) administration, there was a 5-fold higher molar formation of SN-38 lactone compared to i.v. (10 mg/kg) administration in tumor and non-tumor-bearing mice. SN-38 systemic exposure associated with the lowest oral dose (25 mg/kg) achieving complete response for HCl was 942.6 ng/ml.h. These results emphasize the importance of pharmacokinetic studies as part of tumor response studies in xenograft models.

L53 ANSWER 34 OF 83

MEDLINE

DUPLICATE 18

AB **Irinotecan**, or **CPT-11** (7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin++), is a water-soluble derivative of camptothecin with promising activity against several types of malignancies. In addition to 7-ethyl-10-hydroxycamptothecin (SN-38), its active metabolite, we were able to identify several metabolites in the plasma of patients treated with this drug, especially an oxidative metabolite, 7-ethyl-10[4-N-(5-aminopentanoic acid)-1-piperidino]

carbonyloxy-camptothecine. During our study of the biosynthesis of 7-ethyl-10[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxy-camptothecine from **CPT-11** by human liver microsomes, we were able to detect another quantitatively important polar metabolite, which was also present in the plasma and urine of patients treated with **CPT-11**. On the basis of preliminary experiments, the structure of this compound was postulated to be 7-ethyl-10-(4-amino-1-piperidino)carbonyloxycamptothecine, and this structure was synthesized by Rhone-Poulenc Rorer. Urine samples and human liver microsomal extracts were studied by high-performance liquid chromatography/atmospheric pressure chemical ionization/tandem mass spectrometry to identify its structure formally. The identification of the metabolite was supported by identical retention time, mass-to-charge ratio and tandem mass spectrometry fragmentation as a synthetic standard. Like **irinotecan**, 7-ethyl-10-(4-amino-1-piperidino)carbonyloxycamptothecine was a weak inhibitor of cell growth of P388 cells in culture (IC<sub>50</sub> = 3.4 micrograms/ml vs. 2.8 micrograms/ml for **irinotecan** and 0.001 microgram/ml for SN-38). It was also a poor inducer of topoisomerase I-DNA cleavable complexes (100-fold less potent than SN-38). However, unlike 7-ethyl-10[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxy-camptothecine, this new metabolite could be hydrolyzed to SN-38 by human liver microsomes and purified human liver **carboxylesterase**, though to a lesser extent than **irinotecan**. This compound can therefore contribute to the activity and toxicity profile of **irinotecan** in vivo.

L53 ANSWER 35 OF 83 MEDLINE DUPLICATE 19  
 AB The antitumor activity of **irinotecan** in vitro primarily results from its hydrolysis by **carboxylesterase** to the active metabolite SN-38. The present study was conducted to evaluate the effect of human neuroblastoma xenografts on **irinotecan** and SN-38 disposition after i.v. and oral **irinotecan** administration. Non-tumor-bearing mice and mice bearing three different human neuroblastoma xenograft lines (NB1691, NB1643, and NBEB) were given **irinotecan** (10 mg/kg) by short i.v. injection into the tail vein or by oral gavage. Serial plasma samples were obtained, processed to isolate **irinotecan** and SN-38 lactone, and assayed with a sensitive and specific high-performance liquid chromatography assay. Noncompartmental and compartmental pharmacokinetic analyses were performed. A four-compartment model was used for analysis of **irinotecan** and SN-38 concentration-time data after i.v. administration. The presence of tumor increased **irinotecan** systemic exposure (1.2-3.8-fold; P < 0.05) after i.v. and oral administration in mice bearing neuroblastoma xenografts compared to non-tumor-bearing mice. Moreover, SN-38 systemic exposures were higher (1.3-3.8-fold; P < 0.05) in mice bearing human neuroblastoma xenografts as compared to non-tumor-bearing mice, with the greatest effect observed after oral administration of **irinotecan**. A schematic model is presented to provide a mechanistic basis for our observations. These results emphasize the need to perform preclinical pharmacokinetic studies to evaluate the influence of tumor on drug disposition.

L53 ANSWER 36 OF 83 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

L53 ANSWER 37 OF 83 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

L53 ANSWER 38 OF 83 MEDLINE DUPLICATE 20  
 AB Five (20S)-10-hydroxycamptothecin derivatives carrying the long-chain fatty acid esters were prepared for the development of a new class of prodrug-type agents. In vitro experiments using three kinds of purified



**carboxylesterase** isozymes from the liver microsomes of rat, pig, and human demonstrated that these derivatives were efficiently metabolized by enzymes compared with **CPT-11**.

L53 ANSWER 39 OF 83 MEDLINE DUPLICATE 21

AB The relevance of P170-glycoprotein (P-gp) and multidrug resistance-associated protein (MRP) for the sensitivity to **CPT-11** was investigated in human malignant cell lines as well as in human tumour xenografts. In vitro, the P-gp-positive sublines BRO/mdr1.1 (transfected with MDR1) and 2780AD were slightly cross-resistant against **carboxylesterase**-activated **CPT-11**. Cross-resistance against SN-38 was present in 2780AD cells, but not in BRO/mdr1.1 cells. The P-gp modulators BIBW22BS, verapamil and dextrageldipine partly reversed the resistance against **CPT-11** in the P-gp-positive sublines. BIBW22BS was the most effective modulator in the reversal of the resistance against **carboxylesterase**-activated **CPT-11** as well as against SN-38 in the 2780AD subline. In contrast to doxorubicin and vincristine, the BRO/mdr1.1 xenografts were at least as sensitive to **CPT-11** as the BRO xenografts. The 2780AD xenografts were slightly less sensitive than the parent tumours, but there was no difference in topoisomerase I DNA unwinding activity. Therefore, the high retention of the multidrug-resistant phenotype of 2780AD cells in vivo may be the cause of the low cross-resistance against **CPT-11**. The MRP-positive subline GLC4/ADR was cross-resistant against **carboxylesterase**-activated **CPT-11** and SN-38. GLC4/ADR cells, however, demonstrated a twofold lower topoisomerase I activity than GLC4 cells. Cross-resistance against the camptothecin derivatives was not apparent in the MRP-transfected subline of SW1573/S1. In conclusion, P-gp-positive cells show a low cross-resistance against **CPT-11**/SN38, which is only apparent with high P-gp expression in vivo. MRP does not seem to play a role in the sensitivity to **CPT-11**.

L53 ANSWER 42 OF 83 SCISEARCH COPYRIGHT 2002 ISI (R)

AB **Carboxylesterases** are a ubiquitous class of enzymes thought to be involved in xenobiotic metabolism and detoxification. Primary amino acid sequence data suggest that these proteins localize to the endoplasmic reticulum. However, since this family of proteins is highly homologous, the generation of specific reagents to monitor expression and subcellular localization has been unsuccessful. To accomplish in situ detection of a human alveolar macrophage **carboxylesterase** and a rabbit liver **carboxylesterase**, we constructed plasmids that expressed recombinant proteins containing an 11 amino acid influenza hemagglutinin tag near the C-terminus. These proteins retained **carboxylesterase** activity as determined by the conversion of o-nitrophenol acetate to o-nitrophenol. Following transfection of plasmids encoding these proteins into mammalian cells, cells were analyzed by both fluorescence and electron microscopy. The tagged enzymes were localized to the endoplasmic reticulum of both Cos7 monkey kidney cells and Rh30 human rhabdomyosarcoma cells. No tagged protein was detectable in the culture media. Hence, epitope tagging allowed the analysis of expression and localization of specific **carboxylesterases**. The methods described in this paper are, therefore, applicable to any protein, including those that are highly homologous to other candidate molecules. (C) 1998 Wiley-Liss, Inc.

L53 ANSWER 45 OF 83 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

L53 ANSWER 48 OF 83 MEDLINE DUPLICATE 25

AB **CPT-11** [7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin ] is a prodrug that is converted to the active metabolite SN-38 by **carboxylesterases**. In its active form, the drug inhibits topoisomerase I, causes DNA damage, and induces apoptosis. Data in this study show metabolism of **CPT-11** to SN-38 (7-ethyl-10-hydroxycamptothecin) by a rabbit liver **carboxylesterase** in vitro and growth-inhibitory activity of the products of the reaction. Additionally, stable expression of the cDNA encoding this protein in Rh30 human rhabdomyosarcoma cells increased the sensitivity of the cells to **CPT-11** 8.1-fold. We propose that this prodrug/enzyme combination can be exploited therapeutically in a manner analogous to approaches currently under investigation with the combinations of ganciclovir/herpes simplex virus thymidine kinase and 5-fluorocytosine/cytosine deaminase.

L53 ANSWER 51 OF 83 MEDLINE DUPLICATE 28

AB Human hepatic microsomes were used to investigate the **carboxylesterase**-mediated bioactivation of **CPT-11** to the active metabolite, SN-38. SN-38 formation velocity was determined by HPLC over a concentration range of 0.25-200 microM **CPT-11**. Biphasic Eadie Hofstee plots were observed in seven donors, suggesting that two isoforms catalyzed the reaction. Analysis by nonlinear least squares regression gave KM estimates of 129-164 microM with a Vmax of 5.3-17 pmol/mg/min for the low affinity isoform. The high affinity isoform had KM estimates of 1.4-3.9 microM with Vmax of 1.2-2.6 pmol/mg/min. The low KM **carboxylesterase** may be the main contributor to SN-38 formation at clinically relevant hepatic concentrations of **CPT-11**. Using standard incubation conditions, the effects of potential inhibitors of **carboxylesterase**-mediated **CPT-11** hydrolysis were evaluated at concentrations  $\geq 21$  microM. Positive controls bis-nitrophenylphosphate (BNPP) and physostigmine decreased **CPT-11** hydrolysis to 1.3-3.3% and 23% of control values, respectively. Caffeine, acetylsalicylic acid, coumarin, cisplatin, ethanol, dexamethasone, 5-fluorouracil, loperamide, and prochlorperazine had no statistically significant effect on **CPT-11** hydrolysis. Small decreases were observed with metoclopramide (91% of control), acetaminophen (93% of control), probenecid (87% of control), and fluoride (91% of control). Of the compounds tested above, based on these in vitro data, only the potent inhibitors of **carboxylesterase** (BNPP, physostigmine) have the potential to inhibit **CPT-11** bioactivation if administered concurrently. The **carboxylesterase**-mediated hydrolysis of alpha-naphthyl acetate (alpha-NA) was used to determine whether **CPT-11** was an inhibitor of hydrolysis of high turnover substrates of **carboxylesterases**. Inhibition of alpha-NA hydrolysis by **CPT-11** was determined relative to positive controls BNPP and NaF. Incubation with microsomes pretreated with **CPT-11** (80-440 microM) decreased alpha-naphthol formation to approximately 80% of control at alpha-NA concentrations of 50-800 microM. The inhibitors BNPP (360 microM) and NaF (500 microM) inhibited alpha-naphthol formation to 9-10% of control and to 14-20% of control, respectively. Therefore, **CPT-11**-sensitive **carboxylesterase** isoforms may account for only 20% of total alpha-NA hydrolases. Thus, **CPT-11** is unlikely to significantly inhibit high turnover, nonselective substrates of **carboxylesterases**.

L53 ANSWER 52 OF 83 CANCERLIT

AB The novel anticancer agent, **CPT-11**, is active against

various cancers, and **CPT-11** is a prodrug converted to its active form, SN-38, by **carboxylesterase** in the liver and blood. Since treating patients with non small cell lung cancer (NSCLC) with **CPT-11** is very desirable if NSCLC cells have the ability to convert **CPT-11** to SN-38, we investigated the appearance of **carboxylesterase** in NSCLC cells, and the ability of these cells to convert **CPT-11** to SN-38 using surgically removed samples and cultured cells. High performance liquid chromatography was used to measure **CPT-11** and SN-38 in plasma and medium. **Carboxylesterase** was stained using anti-human **carboxylesterase** polyclonal antibody by an indirect immunostaining method. The cytotoxic effects of **CPT-11** and SN-38 were measured by MTT assay. The pharmacological parameters of **CPT-11** and SN-38 showed no difference between patients with adenocarcinoma (n=16) and those with squamous cell carcinoma (n=5) after intravenous injection of 90 mg/m<sup>2</sup> **CPT-11** for 1 h. Macrophages, endothelial cells of the vessel, fibroblasts, and bronchial ciliated columnar cells were stained with anti-**carboxylesterase** antibodies. Of ten squamous cell carcinomas, seven were strongly positive (++), and three were negative for **carboxylesterase**. Of thirteen adenocarcinomas, two were ++ positive, ten were + positive, and one was negative for **carboxylesterase**. Thus, squamous cell carcinoma showed significantly higher **carboxylesterase** levels more than adenocarcinoma cells (p less than 0.05). When ten human lung cancer cell lines were exposed to 10 uM **CPT-11** during various periods, the SN-38 levels in the cultured medium significantly increased from 1.54 +/- 0.22 ng/mL (mean +/- S.D.) after 1 h to 2.65 +/- 0.47 ng/mL after 24 h (p less than 0.01). The proportion of IC<sub>50</sub>s after 4 h exposure to **CPT-11** to those after 24 h exposure was 7.07 +/- 2.95 (mean +/- S.D.). From these results, we conclude that human lung cancer cells can activate **CPT-11** to SN-38 by themselves, leading to an efficacy of **CPT-11** beyond expectations. (C) American Society of Clinical Oncology 1997.

L53 ANSWER 54 OF 83 MEDLINE DUPLICATE 29  
 AB **CPT-11**, a new semisynthetic derivative of camptothecin, is active in a number of tumor types in the clinic, including colon cancer. **CPT-11** is a drug that is converted into the active metabolite SN-38 by a **carboxylesterase**. Experiments were performed to obtain more insight in the cellular characteristics in 5 unselected human colon-cancer cell lines that account for the differential sensitivity to **CPT-11** and SN-38. In vitro, the sensitivity to **CPT-11** and SN-38 was highest in LS174T and COLO 320 cells, intermediate in SW1398 cells and lowest in COLO 205 and WiDr cells. SN-38 was 130 to 570 times more active than **CPT-11**. **CPT-11** induced complete remissions in 6 out of 12 COLO 320 tumors grown as subcutaneous xenografts, but was not effective in WiDr tumors. The cellular **carboxylesterase** activity did not relate to the sensitivity to **CPT-11**. The enzyme activity was higher in normal mouse tissues, i.e., serum and liver, than in COLO 320 or WiDr xenografts, indicating that tumor **carboxylesterase** is of minor importance for **CPT-11** efficacy. The topoisomerase-1 mRNA expression in tumor cells was not predictive of the antiproliferative effects of **CPT-11** or SN-38. We observed a positive relationship between the DNA topoisomerase-1 activity and the cellular sensitivity to **carboxylesterase**-activated **CPT-11** (r = 0.75, p < 0.1) as well as to SN-38 (r = 0.89, p < 0.05).

The higher topoisomerase-1 activity in COLO 320 cells and tumors when compared with that in WiDr cells and tumors reflected the differences in sensitivity to the drug(s). In conclusion, the DNA topoisomerase-1 activity was the best determinant for **CPT-11/SN-38** sensitivity in this panel of unselected human colon-cancer cell lines.

L53 ANSWER 55 OF 83 MEDLINE DUPLICATE 30

AB **Irinotecan (CPT-11)** is a new camptothecine derivative presently in development for the treatment of several advanced malignancies. It is converted in vivo to a highly potent metabolite, SN-38, by **carboxylesterases**. All camptothecine derivatives undergo lactonolysis in a pH-dependent reversible manner, generating inactive carboxylate forms. We have investigated in vitro the kinetics of transformation of **CPT-11** to SN-38 by human liver microsomes originating from several donors. Microsomes from seven livers were studied individually or as a pooled preparation. **CPT-11**, either in its lactone or its carboxylate form, was added at a range of concentrations. The SN-38 formed was measured by HPLC with fluorometric detection. In the deacylation-limited **carboxylesterase** reaction, the linear steady-state kinetics between 10 and 60 min were determined. At all concentrations of **CPT-11**, the steady-state velocity of SN-38 formation as well as the intercept concentrations of SN-38 were about 2-fold higher when the substrate was under the lactone form than under the carboxylate form. We estimated the values (+/-SD) of K'm and Vmax to be 23.3 +/- 5.3 microM and 1.43 +/- 0.15 pmol/min/mg for the lactone and 48.9 +/- 5.5 microM and 1.09 +/- 0.06 pmol/min/mg for the carboxylate form of **CPT-11**, respectively. We conclude that the greater rate of conversion of **CPT-11** lactone may contribute to the plasma predominance of SN-38 lactone observed in vivo. The inter-individual variation of SN-38 formation was relatively high (ratio of 4 between extreme values) but no large age- or gender-related differences were seen. The effect of twelve drugs of different therapeutic classes (antibiotics, antiemetics, antineoplastics, antidiarrhoeics, analgesics), which could be administered in association with **irinotecan** in the clinical setting, was evaluated in this system (drug concentration: 100 microM; **CPT-11** lactone concentration: 10 microM). Loperamide and ciprofloxacin were the only drugs exerting a weak inhibition of **CPT-11** conversion to SN-38.

L53 ANSWER 62 OF 83 MEDLINE DUPLICATE 34

AB Paclitaxel-2-ethylcarbonate (PC) is a prototype for a family of paclitaxel prodrugs that have significant levels of antitumor activities in rodent models for human cancer. In this study, an enzyme responsible for the conversion of PC to paclitaxel was purified from rat serum. N-terminal amino acid sequence analysis indicated that the isolated enzyme was rat serum **carboxylesterase**. This enzyme was shown to significantly enhance the cytotoxic activities of both PC and 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (**CPT-11**), a water-soluble analogue of camptothecin, on lung carcinoma and melanoma cell lines. Rat serum **carboxylesterase** may have applications for the site-specific delivery of anticancer drugs to tumor masses.

L53 ANSWER 64 OF 83 MEDLINE DUPLICATE 35

AB We have investigated the conversion of the novel anti-topoisomerase I agent **CPT-11 (irinotecan; 7-ethyl-10[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin)** to its

active metabolite, SN-38 (7-ethyl-10-hydroxycamptothecin), by human liver **carboxylesterase** (HLC). Production of SN-38 was relatively inefficient and was enzyme deacylation rate-limited with a steady-state phase occurring after 15-20 min of incubation. This later phase followed Michaelis-Menten kinetics with an apparent  $K_m$  of  $52.9 \pm 5.9$   $\mu\text{M}$  and a specific activity of  $200 \pm 10$   $\mu\text{mol/sec/mol}$ . However, the total enzyme concentration estimated from the intercept concentrations of SN-38 was much lower than that estimated directly from the titration of active sites with paraoxon ( $0.65$  vs.  $2.0$   $\mu\text{M}$ , respectively). Because deacylation rate-limiting kinetics result in the accumulation of inactive acyl-enzyme complex, we postulated that incubation of **CPT-11** with HLC would result in an inhibition of the HLC-catalysed hydrolysis of p-nitrophenylacetate (p-NPA), an excellent substrate for this enzyme. Indeed, this was found to be the case although complete inhibition could not be attained. Analysis of possible kinetic schemes revealed that the most likely explanation for the disparity in estimated enzyme concentrations and the incomplete inhibition of p-NPA hydrolysis is that **CPT-11** also interacts at a modulator site on the enzyme, which profoundly reduces substrate hydrolysis. Furthermore, loperamide, a drug often used for the treatment of **CPT-11**-associated diarrhea, was found to inhibit both **CPT-11** and p-NPA HLC-catalysed hydrolysis, most likely by a similar interaction. These observations have direct implications for the clinical use of **CPT-11**.

L53 ANSWER 65 OF 83 MEDLINE DUPLICATE 36  
 AB 1. **Irinotecan** (also known as **CPT-11**) is a water soluble, semi-synthetic analogue of 20(S)camptothecin (CPT) with promising activity against a range of tumour types. 2. As with all other active analogues of CPT, **irinotecan** causes cell toxicity by stabilizing a ternary complex between the nuclear enzyme topoisomerase I (topo I) and double-stranded DNA. This leads to replication fork-arrest, double DNA strand breaks and, possibly, illegitimate recombination of vital genes. 3. This activity is much greater for its metabolite SN-38 and **irinotecan** is widely considered to be a prodrug of SN-38. 4. The anti-topo I activity of CPT is stereoselective at C-20 and **irinotecan** is synthesized from 20(S)CPT to ensure maximal activity. In aqueous solutions, the lactone ring of CPT undergoes reversible and spontaneous hydrolysis to a ring-opened and inactive carboxylate form. In patients, it has been shown that the lactone is the predominant form of SN-38 in plasma, whereas the opposite is true for **irinotecan**. 5. The transformation of **irinotecan** to SN-38 is catalysed by **carboxylesterases**. However, this conversion appears relatively inefficient in man. 6. **Irinotecan** and SN-38 show evidence of other metabolic reactions (type I and II), some of which could be subject to pharmacogenetic variability. 7. Therapy with **irinotecan** is associated with unusual toxicities, such as an acute cholinergic-like syndrome and delayed onset diarrhoea. Although the mechanism for the diarrhoea remains to be defined, the cholinergic toxicity appears to be due to an inhibition of acetylcholinesterase.

L53 ANSWER 69 OF 83 MEDLINE DUPLICATE 38  
 AB **CPT-11** is a new agent with a unique mechanism of action, namely the inhibition of topoisomerase I. An examination of data from the laboratory reveals several leads which should be pursued in the clinic. A dose-response effect for **CPT-11** activity has been noted in the human tumour cloning assay. **CPT-11** has activity against breast and mesothelioma colony-forming units in a human tumour cloning assay, and has in vivo activity against a number of

paediatric malignancies. Promising combinations in preclinical in vivo models include **CPT-11**/mitomycin C and **CPT-11**/cytosine arabinoside. There is incomplete cross-resistance among topoisomerase I inhibitors, suggesting that combinations of topoisomerase I inhibitors should be investigated. Several natural products have been identified which have potential to decrease **CPT-11**-induced diarrhoea. The level of **carboxylesterase** in a patient's tumour appears to be related to the in vitro activity of **CPT-11**, suggesting that measurement of **carboxylesterase** in a patient's tumour could be used to identify patients who are most likely to respond to treatment with **CPT-11**. These preclinical findings suggest substantial further clinical potential for **CPT-11** in terms of decreased **CPT-11**-induced diarrhoea as well as increased antitumour activity, which should be explored in phase I and II studies.

L53 ANSWER 75 OF 83 MEDLINE DUPLICATE 41  
 AB A hydrolytic enzyme which catalyzes hydrolysis of the ester-linkage of a series of 17-O-acyl derivatives of 7-ethylcamptothecin-21-(2-dimethylamino)ethylamide [acyl derivatives of 22E] was purified from rat liver and its properties were characterized. It hydrolyzed the ester-linkage of all 22E derivatives tested as well as p-nitrophenyl acetate at pH 8-9 but had no effect on 7-ethyl-10-[4-(piperidino)-1-piperidino] carbonyloxycamptothecin (**CPT-11**: **irinotecan**), unlike **CPT-11** converting **carboxylesterase**, which was previously purified from rat serum [Tsuji T. et al., J. Pharmacobio-Dyn., 14, 341 (1991)]. The enzyme had no effect on either acetyl choline or butyrylcholine. It was inhibited by several organophosphorous compounds such as diisopropyl fluorophosphate (DFP), bis-(p-nitrophenyl)phosphate and paraoxon, but was insensitive to inhibitors specific for choline esterases. These results indicate that this liver esterase is clearly distinct from choline esterase and serum **CPT-11** converting enzyme and is able to convert pro-drugs, O-acyl derivatives of 22E, to an antitumor agent.

L53 ANSWER 78 OF 83 MEDLINE DUPLICATE 43  
 AB We measured the plasma concentrations of 7-ethyl-10-[4-(1-piperidino)-1-piperidine]carbonyloxycamptothecin (**CPT-11**) and the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38), after treatment with **CPT-11** to rats pretreated with bis-p-nitrophenylphosphate (BNPP) which is a specific inhibitor of **carboxylesterase**, and non-pretreated rats. The plasma level of SN-38 was decreased in the BNPP-pretreated group compared with those of non-pretreated group, indicating that the esterase involved in **CPT-11** metabolism is a **carboxylesterase**. We also characterized the molecular species of **carboxylesterase** involved in **CPT-11** metabolism using enzyme preparations purified from liver microsomes. Thirteen **carboxylesterase** isozyme activities towards **CPT-11** were compared and guinea pig GLP1 was found to have the highest activity, while human HU1 isozyme had relatively lower activity than those of animal species. In studies on the kinetic parameters of the hydrolysis of **CPT-11** by the purified **carboxylesterase** isozymes the highest Vmax value of the isozymes was found in human HU1 and the smallest was seen in rat RL1. The Vmax/Km for RL1 showed the largest value of 21.7 nmol/mg protein/mM.

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L53 ANSWER 80 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.  
 AB The topoisomerase I inhibitors are an exciting new class of antineoplastic agents currently under clinical development. Analogues of camptothecin with improved toxicity profiles and antitumor activity included **CPT-11** and topotecan. **CPT-11** has demonstrated activity against a variety of tumor types, particularly colon and lung cancer. Early results with topotecan against ovarian and lung cancer are also encouraging. Combination trials with other antineoplastic agents including cisplatin and etoposide, and early clinical trials with new topoisomerase I inhibitors, such as 9-aminocamptothecin, are underway.

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L53 ANSWER 83 OF 83 MEDLINE DUPLICATE 44  
 AB A rat serum enzyme that catalyzes the conversion of a pro-drug, 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin (**CPT-11**), to an anticancer drug, 7-ethyl-10-hydroxycamptothecin (SN-38), was purified and its properties were characterized. The enzyme was purified by column chromatography on diethylaminoethyl Toyopearl 650M, QAE-Sephadex, Sephadex G-150, Con A-Sepharose and high performance liquid chromatography with an ion-exchanger column. It was most active at pH 7.5 and was stable at pH 4-9 for 1 h at 30 degrees C. The molecular weight was estimated to be 60 and 57 kDa by gel filtration and sodium dodecylsulfate-polyacrylamide gel electrophoresis methods, respectively, and the isoelectric point was 4.6, as determined by isoelectric focusing. The Km value for **CPT-11** was 0.28 microM. This enzyme was inhibited by diisopropyl phosphorofluoridate (DFP) and phenylmethanesulfonyl fluoride (PMSF) but insensitive to eserine, p-chloromercuribenzoate (PCMB) and ethylenediaminetetraacetate (EDTA). The enzyme also hydrolyzed p-nitrophenylacetate (p-NPA), a commonly used substrate for esterases, but was not active toward acetylcholine, suggesting that the enzyme is a **carboxylesterase**[EC 3.1.1.1]. During the hydrolyses of **CPT-11** and p-NPA, an initial burst phenomenon similar to that found in the alpha-chymotrypsin-catalyzed hydrolysis of p-NPA was observed. Kinetic analysis revealed that the deacylation of the enzyme is the rate-limiting step in substrate hydrolysis. This enzyme was found to also split other ester derivatives of SN-38 besides **CPT-11**.

=> log y

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

122.64

122.85

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